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FORMULATION AND EVALUATION OF NANOEMULSION FROM PAPAYA LEAF EXTRACT (*Carica Papaya* L.) WITH VARIATION CONCENTRATION OF TWEEN 80

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Abstract

Introduction: Nanoemulsion with small particle size can resolve less effective absorption of drugs. This preparation can be combined with Papaya leaf which can be efficacious as antibacterial because it contains alkaloid, flavonoid, saponin and tannin. The purpose of this study is to determine physical stability of nanoemulsion from Papaya leaf extract.

Method: Formulation of nanoemulsion based on variation concentrations of tween 80, F1 (36%), F2 (37%) and F3 (38%) with evaluation such as organoleptic test, pH test, viscosity test, transmission test, particle size test, Polydispersity Index (PI) test and physical stability test by centrifugation and freeze thawing which use cold temperature (4°C) and room temperature (25°C).

Results: All formulas were stable and met the requirements for evaluation of nanoemulsion with pH value 6,27-6,42; viscosity 1083-3250 Cp; transmission 90,83-97,03%; particle size 14,43-15,43 nm; PI 0,365-0,440.

Conclusion: All formulas had good physical stability and the best formula was F1 tween 80 36% because it had the smallest particle size and Polydispersity Index (PI) value, they were 14,43 nm and 0,365.

Keywords: Nanoemulsion, Papaya Leaf Extract, Physical Stability Test, Tween 80

INTRODUCTION

The development of drug delivery systems in the pharmaceutical sector has been carried out for several years. However, new problems began to emerge such as the ineffective absorption of drugs in the body. It is due to the low solubility of the drug and the size of the molecule is too large so that it is difficult to penetrate the absorption barrier (Ramadon and Mun'im, 2016). Drugs with a poor absorption rate will be wasted in the body. The impact is a low bioavailability (blood level of the drug) and can lead to failure of the drug's therapeutic effect (Permatasari et al., 2016). These problems cause the need for research on formulations that help drug delivery systems become more effective, which is by increasing drug absorption. The development of this nanotechnology system formulation can be used as one way to overcome these problems. One example of a nanotechnology system is nanoemulsion where the active substance is made in nano size (1-100 nm) (Larasati and Jusnita, 2020). Nanoemulsion consist of water, oil, surfactants and cosurfactants. Tween 80 surfactant with a concentration of 38% can be stable in nanoemulsion (Arianto and Cindy 2019). In addition to containing these components, nanoemulsion can also be combined with natural ingredients, one of which is Papaya leaf (Carica papaya L.) which has antibacterial properties because it contains alkaloids, flavonoids, saponins and tannins (Cahyanta et al., 2020). At concentration of 0,3%, Papaya leaf extract can be efficacious as an inhibitor of bacterial growth (Callixte et al., 2020). Based on several studies that have been carried out and see the advantages of nanoemulsion, the researcher is interested in conducting research on the formulation and evaluation of nanoemulsion from 96% ethanol extract of Papaya leaf (Carica papaya L.) with variations of tween 80 base with concentrations of 36%, 37% and 38%.

METHOD

A. Research Design

This research used an experimental design with descriptive analysis method.

B. Research Location and Time

This research was conducted at the Pharmaceutical Technology Laboratory of STIKes Mitra Keluarga Bekasi in February-March 2022.

C. Population and Sample

The population and sample in this study were Papaya leaf (Carica papaya L.) which were obtained from a supplier of extracts Palapa Muda Perkasa, Depok.

D. Research variable

The variable in this study was independent variable because the variable was not compared to other variables (Heri and Sriartha, 2019). The independent variables in this study were organoleptic, pH, viscosity, transmittance, particle size, Polydispersity Index (PI) and physical stability.

E. Research Tools

The tools used were rotary evaporator, analytical balance (Ohaus SPX222 Scout), brookfield viscometer (LV 801), digital pH meter (ATC), UV-Vis spectrophotometer, mixer (IKA RW 20), hot plate (IKA C-MAG), centrifugator, sonicator (Power Sonic405), particle size analyzer (Horiba SZ-100), refrigerator (Showcase), beaker glass (Iwaki Pyrex®), measuring cup (Iwaki Pyrex®), porcelain crucible (Iwaki Pyrex®), watch glass (Iwaki Pyrex®), glass bottle, spatula, dropper pipette, stirring rod.

F. Research Material

The ingredients used were 96% ethanol extract of Papaya leaf, sunflower oil (Kimia Jaya), tween 80 (Kimia Jaya), sorbitol (Samudra Kimia), methyl paraben (Kimia Jaya), propyl paraben (Kimia Jaya), 96% ethanol (Merck) and aquadest (Kimia Jaya).

G. Procedure

1. Papaya Leaf Preparation

The sample selection was done by purposive sampling method, which was a sampling method where the researcher determined the criteria for the sample to be used (Etikan and Bala, 2017). The criteria for a good sample were dark green and fresh Papaya leaf aged 2-5 months after planting (Roni et al., 2019). Papaya leaf samples were washed, wet sorting, chopping, drying, dry sorting and pollination (Febriansah, 2017).

2. Papaya Leaf Determination

Determination of plant served to ensure the truth and know the identity of the plant (Puspitasari and Proyogo, 2017). Plant determination was carried out at the Bogorinse Herbarium, LIPI Bogor.

3. Papaya Leaf Extraction

Papaya leaf was extracted by maceration method. 1000 g of Papaya leaf simplicia powder was macerated by soaking it in 5 L of 96% ethanol. The powder was soaked for 3 days at room temperature (25-30°C). Further, the extract was filtered. The filtrate obtained from the maceration process then concentrated with rotary evaporator at temperature 50°C to remove unwanted solvents in order to obtain 100 g thick extract of Papaya leaf (Pradiningsih and Mahida, 2019).

4. Papaya Leaf Phytochemical Screening

a. Alkaloid Test

50 mg of extract was dissolved in 1 mL of 2 M HCl then filtered. The filtrate was added 1 drop of Mayer, Wagner and Dragendorff reagents in different test tubes. If the extract was

positive for alkaloids, a white precipitate would be formed in the Mayer reagent, a brown precipitate in the Wagner reagent and an orange precipitate in the Dragendorff reagent.

b. Flavonoid Test

40 mg of extract added 100 mL of aquadest, boiled for 15 minutes then filtered. After that, 0,05 mg of Mg powder and 1 mL of HCl were added to 5 mL of the filtrate and the mixture was shaken vigorously. If the extract was positive for flavonoids, an orange color would be formed.

c. Saponin Test

5 mL of extract was added with aquadest and shaken vigorously. Let it stand for 10 minutes, added 1 drop of 2 N HCl. If a stable foam was formed for 10 minutes, then the extract was positive for saponins.

d. Tanin Test

0,1 g of extract was added to 10 mL of aquadest and filtered. 5 mL of 1% FeCl3 was added to the filtrate. If a dark blue or black color was formed, then the extract was positive for tannins.

5. Formulation of Papaya Leaf Extract Nanoemulsion

Nanoemulsion was made by dissolving sunflower oil with some sorbitol. The remaining sorbitol was used to dissolve the Papaya leaf extract. This solution was mixed with a solution of sunflower oil and sorbitol and then homogenized (mixture 1). The aqueous phase was made by dissolving methyl paraben and propyl paraben with aquadest and then heated using a hot plate. The solution was cooled and added tween 80 with different concentrations 36%, 37% and 38% in each formula (mixture 2). This mixture was homogenized manually with a stirring rod. Mixture 1 and mixture 2 were homogenized with mixer at speed 450 rpm for 15 minutes. After that, the nanoemulsion was sonicated for 2 hours to remove the formed foam (Arianto and Cindy, 2019). Papaya leaf extract nanoemulsion formula can be seen in table 1.

Table 1. Papaya Leaf Extract Nanoemulsion Formula

Material Composition	Nanoemulsion Formula (%w/v)			Function
	F1	F2	F3	
Papaya leaf extract	0,5	0,5	0,5	Antibacterial
Sunflower oil	5	5	5	Oil phase
Tween 80	36	37	38	Surfactant
Sorbitol	22	22	22	Cosurfactant
Methyl paraben	0,1	0,1	0,1	Preservative
Propyl paraben	0,02	0,02	0,02	Preservative
Aquadest ad	100	100	100	Solvent

6. Evaluation of Papaya Leaf Extract Nanoemulsion

a. Organoleptic Test

Organoleptic test was carried out by observing the color, aroma and phase separation of the nanoemulsion stored at room temperature (25±2°C) for 14 days (Arianto and Cindy, 2019).

b. pH Test

This test was carried out using a pH meter by inserting the pH meter into the nanoemulsion which was stored at room temperature (25±2°C) for 14 days (Arianto and Cindy, 2019). The pH requirements of the preparation were adjusted to a safe pH for the skin, which was 4-10 (BSN, 2017).

c. Viscosity Test

Viscosity test was carried out using a brookfield viscometer. The nanoemulsion viscosity was measured with spindle number 4 at a speed of 12 rpm. This test was carried out on nanoemulsion stored at room temperature (25±2°C) for 14 days (Larasati and Jusnita, 2020). The viscosity of the nanoemulsion was adjusted to the viscosity of the topical preparation, which was 500-5000 Cp (Robert, 2020).

d. Transmittance Test

Transmittance test was carried out by dissolving 2 mL of nanoemulsion in 100 mL of aquadest, tested using a UV-Vis spectrophotometer at wavelength 650 nm (Pratiwi et al., 2017). This test was carried out on the first day of the nanoemulsion formulation. The transmission test requirement of nanoemulsion was 80-100% (FDA, 2020).

e. Particle Size Test

This test was carried out using Particle Size Analyzer (PSA) to determine the particle size of nanoemulsion (Prasetya et al., 2019). This test was carried out on the first day of the nanoemulsion formulation. 2 mL of nanoemulsion was dissolved in 100 mL of distilled water and the samples were tested at the Integrated Laboratory Research Center (ILRC), University of Indonesia. The nanoemulsion particle size requirement was 1-100 nm (FDA, 2020).

f. Polydispersity Index (PI) Test

This test was carried out using Particle Size Analyzer (PSA) to determine the particle size distribution of nanoemulsion. Sample preparation for this test was the same as for particle size testing. The Polydispersity Index (PI) requirement was <0,5 (Marzuki et al., 2019).

g. Physical Stability Test

1) Centrifugation Test

This test was carried out to observe the stability of nanoemulsion using a centrifuge with a rotation speed 3000 rpm for 30 minutes (Iskandar et al., 2021).

2) Freeze Thawing Test

This test was carried out by observing the stability of nanoemulsion at low temperature (4±2°C) for 24 hours and then transferred to room temperature (25±2°C) for 24 hours (1 cycle). This test was carried out for 6 cycles (Forestryana et al., 2020).

RESULTS

A. Determination Results of Papaya Leaf

Plant determination was carried out at the Bogorinse Herbarium, LIPI Bogor. Based on the results of the determination, it can be seen that the Papaya leaf used as a sample was a type of Carica papaya (L.) with the family Caricaceae.

B. Phytochemical Screening Results of Papaya Leaf Extract

Based on the results of phytochemical screening, it can be seen that the alkaloid test, saponin test and tannin test showed positive results, while the flavonoid test showed negative results.

C. Organoleptic Test Results of Papaya Leaf Extract Nanoemulsion

The best formula was formula 3 with the lightest color. The results of the Papaya leaf nanoemulsion organoleptic test can be seen in table 2.

Table 2. Papaya Leaf Extract Nanoemulsion Organoleptic Test

Formula	Color	Aroma	Phase Separation
F1	Clear, dark greenish yellow	Papaya leaf	No Separation
F2	Clear, slightly dark greenish yellow	Papaya leaf	No Separation
F3	Clear, bright greenish yellow	Papaya leaf	No Separation

Information :

F1 : Papaya extract leaf nanoemulsion with tween 80 36%
F2 : Papaya extract leaf nanoemulsion with tween 80 37%
F3 : Papaya extract leaf nanoemulsion with tween 80 38%

D. pH Test Results of Papaya Leaf Extract Nanoemulsion

All formulas were stable and complied with the skin's pH requirements. The results of the Papaya leaf nanoemulsion pH test can be seen in table 3.

Table 3. Papaya Leaf Extract Nanoemulsion pH Test

Day	pH		
	F1	F2	F3
	Average ± SD	Average ± SD	Average ± SD
0	6,27 ± 0,02	6,35 ± 0,02	6,42 ± 0,02
7	6,27 ± 0,02	6,35 ± 0,02	6,42 ± 0,02
14	6,27 ± 0,02	6,35 ± 0,02	6,42 ± 0,02

Information :
F1 : Papaya extract leaf nanoemulsion with tween 80 36%
F2 : Papaya extract leaf nanoemulsion with tween 80 37%
F3 : Papaya extract leaf nanoemulsion with tween 80 38%

E. Viscosity Test Results of Papaya Leaf Extract Nanoemulsion

The results of viscosity test showed that all formulas were in accordance with the viscosity requirements of topical preparations. The results of the Papaya leaf nanoemulsion viscosity test can be seen in table 4.

Table 4. Papaya Leaf Extract Nanoemulsion Viscosity Test

Day	Viscosity (Cp)		
	F1	F2	F3
	Average ± SD	Average ± SD	Average ± SD
0	1167 ± 144,34	2917 ± 144,34	3250 ± 250,00
7	1083 ± 144,34	2750 ± 250,00	3000 ± 250,00
14	1083 ± 144,34	2667 ± 144,34	2883 ± 144,34

Information :
F1 : Papaya extract leaf nanoemulsion with tween 80 36%
F2 : Papaya extract leaf nanoemulsion with tween 80 37%
F3 : Papaya extract leaf nanoemulsion with tween 80 38%

F. Transmission Test Results of Papaya Leaf Extract Nanoemulsion

Formula with the best transmittance percentage was formula 3. The results of the Papaya leaf nanoemulsion transmittance test can be seen in table 5.

Table 5. Papaya Leaf Extract Nanoemulsion Transmittance Test

Formula	Transmittance (%)
	Average ± SD
F1	90,83 ± 0,01
F2	93,23 ± 0,00
F3	97,03 ± 0,01

Information :
F1 : Papaya extract leaf nanoemulsion with tween 80 36%
F2 : Papaya extract leaf nanoemulsion with tween 80 37%
F3 : Papaya extract leaf nanoemulsion with tween 80 38%

G. Particle Size Test Results of Papaya Leaf Extract Nanoemulsion

Based on the particle size test, the best formula was formula 1. The results of the Papaya leaf nanoemulsion particle size test can be seen in table 6.

Table 6. Papaya Leaf Extract Nanoemulsion Particle Size Test

Formula	Particle Size (nm)
	Average ± SD
F1	14,43 ± 0,21
F2	15,20 ± 0,35
F3	15,43 ± 0,25

Information :
F1 : Papaya extract leaf nanoemulsion with tween 80 36%
F2 : Papaya extract leaf nanoemulsion with tween 80 37%
F3 : Papaya extract leaf nanoemulsion with tween 80 38%

H. Polydispersity Index (PI) Test Results of Papaya Leaf Extract Nanoemulsion

In the PI test the best formula is formula 1. The results of the Papaya leaf nanoemulsion PI test can be seen in table 7.

Table1. Polydispersity Index (PI) Test of Papaya Leaf Extract Nanoemulsion

Formula	Polydispersity Index (PI)
	Average ± SD
F1	0,365 ± 0,033
F2	0,411 ± 0,025
F3	0,440 ± 0,097

Information :
F1 : Papaya extract leaf nanoemulsion with tween 80 36%
F2 : Papaya extract leaf nanoemulsion with tween 80 37%
F3 : Papaya extract leaf nanoemulsion with tween 80 38%

I. Physical Stability Test Results of Papaya Leaf Nanoemulsion

Papaya leaf nanoemulsion stability test was carried out by centrifugation test and freeze thawing test. Based on the results of the study, it was known that all stable formulas did not occur in the phase separation either in the centrifugation test or in the freeze thawing test.

DISCUSSION

Formulation research and evaluation of Papaya leaf extract (Carica papaya L.) nanoemulsion with variations in concentration of tween 80 aims to obtain the best formula in terms of physical stability of the formulated nanoemulsion. This research was carried out in several stages, which were Papaya leaf sample preparation, Papaya leaf extraction, phytochemical screening of Papaya leaf extract, formulation and evaluation of nanoemulsion from Papaya leaf extract. The evaluations were organoleptic test, pH test, viscosity test, transmittance test, particle size test, Polydispersity Index (PI) test and physical stability test by centrifugation and freeze thawing.

Papaya leaf extraction was carried out with maceration method with 96% ethanol as solvent. The maceration method was chosen because the method is easy, the equipment used was simple and this method was a cold extraction which was suitable for the active substances contained in Papaya leaf which were not resistant to high heating (Julianto, 2019). The 96% ethanol solvent was chosen because it had the same polarity as the active substances contained in Papaya leaf, which was polar. In addition, 96% ethanol was neutral, safe and easy to obtain (Riwanti et al., 2020). The active substances in Papaya leaf to be extracted are alkaloids, flavonoids, saponins and tannins.

In 1000 g of Papaya leaf simplicia powder, 105,4 g of thick dark green extract was obtained, with a distinctive aroma of Papaya leaf with an extract yield of 10,54%. The extract yield was in accordance with the general requirements for extract yields in Farmakope Herbal Indonesia (2017), which is not less than

7,3%. In the research of Octavianni (2016), the yield of the extract was not much different, which was 10,07% with the characteristics of extract were thick dark green color and distinctive aroma of Papaya leaf. This showed that the extract results in this study are in accordance with previous studies.

Phytochemical screening is the initial stage to provide an overview of the class of compounds contained in the plant under study. In this study, phytochemical screening was carried out on the active compounds contained in Papaya leaf, which were alkaloids, flavonoids, saponins and tannins (Cahyanta et al., 2020). In the alkaloid test, the extract was added with HCl and three reagents, which were mayer, wagner and dragendorff. The addition of HCl functioned to dissolve alkaloids from the extract, while the reagents of Mayer, Wagner and Dragendorff functioned to identify alkaloid compounds (Nugrahani et al., 2016).

Alkaloid test with Mayer reagent showed a positive result in the form of a white precipitate. These results are in accordance with the research of Harahap and Situmorang (2021) which also gave a positive result in the presence of a white precipitate. A white precipitate can be formed because the nitrogen ions in the alkaloids bind metal ions K^+ from $K_2[HgI_4]$, this results formation of a potassium-alkaloid complex in the form of a white precipitate (Baharudin, 2017).

In the alkaloid test with Wagner reagent gave positive results indicated by the presence of a brown precipitate. These results are in accordance with the research of Harahap and Situmorang (2021) which showed a positive result with a brown precipitate. The formation of a brown precipitate is caused by the reaction between nitrogen ions in the alkaloids with metal ions K^+ from KI_3 to form a potassium-alkaloid complex in the form of a brown precipitate (Baharudin, 2017).

The alkaloid test with Dragendorff reagent showed a positive result in the form of an orange precipitate. These results are in accordance with the research of Harahap and Situmorang (2021) which also gave a positive result in the presence of an orange precipitate. An orange precipitate can be formed because the nitrogen ions in the alkaloids bind metal ions K^+ from $K[BiI_4]$ This results in the formation of a potassium-alkaloid complex in the form of an orange precipitate (Baharudin, 2017).

Flavonoid testing was carried out by adding aquadest Mg and HCl powder to the extract. Aquadest functions to dissolve flavonoids while Mg and HCl powders function as reagents to identify flavonoid compounds. The results of the flavonoid test in this study were negative because no red color was formed. This result is different from the research of Ramadhani et al (2020) which showed a positive result in the form of a red solution. The formation of a red solution is caused by a reduction reaction caused by Mg and HCl so that a red or orange solution is formed (Nugrahani et al., 2016).

In the saponin test, the extract was added with aquadest and HCl. Aquadest functions to dissolve saponins from the extract and forms foam, while HCl serves to test the stability of the formed foam. The saponin test gave a positive result in the form of a stable foam formation. These results are in accordance with the research of Harahap and Situmorang (2021) which also formed a stable foam. Foam can be formed because the glycosides in the saponin compound are hydrolyzed into glucose and other compounds, the foam will remain stable even though it is reacted with HCl (Nugrahani et al., 2016).

The tannin test was carried out by adding aquadest and $FeCl_3$ on the extract. Aquadest functions to dissolve tannins from extracts and $FeCl_3$ serves to identify the phenol group in tannins. The tannin test gave a positive result in the form of a color change to black. These results are in accordance with the research of Ramadhani et al (2020) indicating a positive result in dark blue or black. This blackish color can be formed due to a complex reaction between the phenol group in tannins and metal ions Fe^{3+} (Baharudin, 2017).

Organoleptic test is a test carried out by observing the physical sample using the senses. Nanoemulsion is said stable if there is no physical change during storage. In table 2, it is known that all formulas have a distinctive Papaya leaf aroma and no phase separation occurs. However, there are color differences in each formula where the higher concentration of tween 80, the green color will fade. This result is different from the research of Arianto and Cindy (2019) which in this study, the nanoemulsion had a clear yellow color because there was no addition of extract.

The occurrence of color differences in each formula can be influenced by the 80% tween concentration. The higher concentration of tween 80%, the color of nanoemulsion will be brighter because tween 80 which is clear yellow will cover the dark green color of Papaya leaf extract. This is in accordance with the literature, where according to Sheskey et al (2017) tween 80 has the characteristics of a clear yellow color and according to Octavianni (2016) which stated that Papaya leaf extract was dark green. The

results of organoleptic test can be seen in table 2.

The pH test is carried out to determine sample acidity degree using pH meter. In this study, the nanoemulsion had a pH value that was not much different from the research of Arianto and Cindy (2019). In that study, the average pH was 6,5. The results of the pH test in this study were in accordance with the standard skin pH requirements 4-10 (BSN, 2017). If the pH is too acidic, it will irritate the skin while a pH that is too alkaline will make the skin dry which can cause scaly skin (Shabrina et al., 2020). Differences pH values in each formula can occur due to differences concentration of tween 80. The higher concentration of tween 80, the pH value will increase because tween 80 has an alkaline pH which is 6-8 (Handayani et al., 2018). The results of pH test can be seen in table 3.

Viscosity test is a test to determine the viscosity of a sample. The viscosity value of nanoemulsion in the study met the requirements because it was in accordance with the viscosity range of topical preparations 500-5000 Cp (Robert, 2020). This result is different from the research of Arianto and Cindy (2019) with an average viscosity of 225 Cp. This happened because in that study there was no addition of extract so the viscosity value was lower.

During 14 days storage at room temperature (25±2°C) all formulas decreased in viscosity value, this can occur due to the influence of temperature during storage. On the other hand, the viscosity value increases with increasing concentration of tween 80. This is in accordance with the research conducted by Zulfa et al (2019) which states that higher concentration of tween 80 had greater ability to reduce the size of the globule diameter so that the globule arrangement becomes denser and uniform. In addition, tween 80 has a thick consistency so it can increase the viscosity of nanoemulsion. The results of viscosity test can be seen in table 4.

The transmittance test is a test to determine the level of clarity of a sample. In this study, all formulas were in accordance with the requirements for transmittance of nanoemulsion because they were in the 80-100% range (FDA, 2020). If the nanoemulsion preparation has a transmittance of more than 80%, it is estimated that the particles formed have reached the nanometer size. The higher transmittance percentage, nanoemulsion will be clearer (Zulfa et al., 2019). The results showed that higher concentration of tween 80 had higher percentage of transmittance. This is because the clear yellow color at tween 80 will cover the dark green color of Papaya leaf extract. Color density can affect the clarity of a nanoemulsion (Jaya et al., 2017). The results in this study are not much different from the researchof Aprilya et al (2021) with an average transmittance of 95,41%. The transmittance test results can be seen in table 5.

The particle size test is the main parameter in nanoemulsion because it states the particle size related to the absorption of the active substance into body. If the particle size gets smaller, it will increase the absorption of the active substance into body (Safrida et al., 2020). The particle size result in this study is different from the research of Arianto and Cindy (2019) which has an average particle size of 124,47 nm. Although different, the particle size in this study met the requirements for the particle size of nanoemulsion, which is 1-100 nm (FDA, 2020). Based on the results of the study, it can be seen that higher concentration of tween 80 had larger particle size. This is presumably due to the interaction between Papaya leaf extract and tween 80 which need further research. The addition of Papaya leaf extract can affect particle size of nanoemulsion. The results of the particle size test can be seen in table 6.

Polydispersity Index (PI) test is a test to determine the uniformity of particle size distribution in the sample. In this study, all formulas met the requirements Polydispersity Index (PI) of nanoemulsion, which is <0,5. If the PI value is smaller, the particle size of the nanoemulsion will be more uniform (Marzuki et al., 2019). These results are not much different from the research of Rusdi (2017) with an average Polydispersity Index (PI) value of 0,370. It can be seen that higher concentration of tween 80 had higher value of the Polydispersity Index (PI). In addition, the results also showed that the uniform distribution of all formulas was monodisperse, it means that the nanoemulsion had a uniform particle size shape (Syukri et al., 2020). The results of the Polydispersity Index (PI) test can be seen in table 7.

Centrifugation test is a test to determine the stability of nanoemulsion preparations. Nanoemulsion is said stable if there is no phase separation after centrifugation. If nanoemulsion is unstable after being centrifuged, it is feared that the nanoemulsion will not be able to withstand the shock effect during the product delivery process (Shabrina et al., 2020). The results of the centrifugation test on all formulas showed no phase separation after centrifugation. These results are in accordance with research conducted by Arianto and Cindy (2019).

Freeze thawing test is a test to determine the stability of nanoemulsion based on temperature changes. Nanoemulsion should remain stable after the freeze thawing test. If it does not meet the requirements of freeze thawing test, it is feared that the nanoemulsion preparation will become unstable due to the influence of temperature during storage (Nurdianti et al., 2018). The result of freeze thawing test on all formulas did not occur phase separation after storage for 6 cycles. These results are in accordance with the research of Arianto and Cindy (2019).

CONCLUSION

Nanoemulsion of 96% ethanol extract Papaya leaf with variation concentrations of tween 80 36%, 37% and 38% had good physical stability. The best formula of extract Papaya leaf nanoemulsion was formula 1 with concentration of tween 80 36% because it had the smallest particle size and PI values, they were 14,43 nm and 0,365.

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